HUMAN VACCINES & IMMUNOTHERAPEUTICS
2022, VOL. 18, NO. 1, e2041945 (6 pages)
https://doi.org/10.1080/21645515.2022.2041945

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SHORT REPORT

Self-Reported safety of the BBIBP-CorV (Sinopharm) COVID-19 vaccine among Iranian people with multiple sclerosis

Masoud Etemadifar[a,b], Amir Parsa Abhari[b,c], Hosein Nouri[b,c], Amirhossein Akhavan Sigari[b], Seyed Mohammad Piran Daliyeh[b], Mohammad Reza Maracy[d], Mehri Salari[e], Shiva Maleki[b], and Nahad Sedaghat[b,c]

[a]Department of Neurosurgery, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran; [b]Alzahra Research Institute, Alzahra University Hospital, Isfahan University of Medical Sciences, Isfahan, Iran; [c]Network of Immunity in Infection, Malignancy, and Autoimmunity (NIIMA), Universal Scientific Education and Research Network (USERN), Iran; [d]Department of Epidemiology and Biostatistics, School of Health, Isfahan University of Medical Sciences, Isfahan, Iran; [e]Functional Neurosurgery Research Center, Shohada Tajrish Comprehensive Neurosurgical Center of Excellence, Shahid Beheshti University of Medical Sciences, Tehran, Iran

ABSTRACT

To affirm the short-term safety of the BBIBP-CorV (Sinopharm) COVID-19 vaccine among people with multiple sclerosis (pwMS), 517 vaccinated and 174 unvaccinated pwMS were interviewed. 16.2% of the vaccinated pwMS reported at least one neurological symptom in their respective vaccine-related at-risk periods (ARP) – a period from the first dose until two weeks after the second dose of the vaccine. In a multivariable logistic regression model, the presence of comorbidities ($P = 0.01$), use of natalizumab ($P = 0.03$), and experiencing post-vaccination myalgia ($P < 0.01$) predicted the development of post-vaccination neurological symptoms. One MS relapse, one COVID-19 contraction, and one ulcerative colitis flare after the first dose, and four MS relapses after the second dose of the vaccine were the only reported serious adverse events during the ARPs. To show if the vaccine provoked MS relapses, we compared the relapse rate of vaccinated pwMS in the vaccine-related ARP with the annualized relapse rate of unvaccinated pwMS in the prior year—a measure of baseline MS relapsing activity in the respective time—using a multivariable Poisson regression model accounting for possible confounders, which failed to show any statistically significant increase ($P = 0.78$). Hence, subject to replication—as the vaccinated and unvaccinated pwMS differed in baseline characteristics—the BBIBP-CorV vaccine does not seem to affect short-term MS activity. Furthermore, as 83.33% of the unvaccinated pwMS reported fear of possible adverse events to be the reason of their vaccination hesitancy, provision of evidence-based consultations to pwMS is encouraged. Limitations of our study briefly included lack of data for self-controlled analysis of relapse rates, possible presence of recall bias, and lack of on-site validations regarding the clinical outcomes due to the remote nature.

ARTICLE HISTORY
Received 9 November 2021
Revised 27 January 2022
Accepted 10 February 2022

KEYWORDS
Multiple sclerosis; SARS-CoV-2, COVID-19 vaccines; vaccine safety; adverse events; BBIBP-CorV

Introduction

More than two years passed the emergence of the coronavirus disease 2019 (COVID-19), several vaccines were developed and approved. The BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), ChAdOx1 (AstraZeneca), Ad26.COV2.S (Johnson and Johnson), CoronaVac (Sinovac), Covaxin (Bharat), Nuvaxovid (Novavax), Covovax (Serum Institute of India), and BBIBP-CorV (Sinopharm) vaccines are currently being used worldwide and all have received authorization from the World Health Organization as of January 2022 (covid19.trackvaccines.org/agency/who/).

Vaccination is considered as the most prominent scheme to halt the rapid surge of COVID-19 and end the pandemic; However, administration of vaccines in people with multiple sclerosis (pwMS) has always been a matter of controversy. These concerns arose considering the potential effect of disease-modifying therapies (DMTs) on the immunogenicity of the vaccines or probable vaccine-associated worsening of the disease course. Theoretically, vaccines may either trigger and increase the risk of MS in healthy individuals, or increase relapses in already-diagnosed pwMS. This theory seems to be more plausible with live attenuated vaccines—such as the yellow fever vaccines[1,2]– than inactivated or other platforms. Nevertheless, no other population-level association has been identified between vaccination and MS development or relapses.[3–5] Moreover, this also seems to be true for COVID-19 vaccines based on the limited data available to date.[6–10] Based on our observations in the clinic, however, pwMS are concerned about the safety of COVID-19 vaccination, considering their disease. Therefore, while also considering that safety concerns may be a major reason of vaccination hesitancy among pwMS, providing them with evidence-based consultations and reasoning has gained more importance.

Inadequate data were available at the time of initiation of this study on the reasons for vaccination hesitancy, and safety of the BBIBP-CorV COVID-19 vaccine in pwMS. Therefore, this preliminary study aimed to investigate the reasons of vaccination hesitancy, and assess the BBIBP-CorV vaccine's short-term safety in a relatively large cohort of pwMS in Iran.

Materials and methods

Following the STROBE guidelines, we report our remote retrospective cohort study. A questionnaire, first created by a team of researchers, was used to collect information from the pwMS. These participants were identified and assessed

CONTACT Nahad Sedaghat nahad.sedaghat@gmail.com Alzahra Research Institute, Alzahra University Hospital, Isfahan University of Medical Sciences, Isfahan, Iran

for eligibility via an online platform (Porsline.ir), distributed in vaccination centers and MS forums across Iran from June 7th until 12th, 2021, in which they entered their information, including their telephone number. A trained nurse collected the information on eligible patients via telephone calls, from June 18th until 24th, 2021. Participants who did not provide their telephone numbers were excluded, as their MS could not be verified. Eligible participants—pwMS with a minimum disease duration of one year who either received the BBIBP-CorV vaccine or no vaccine—went through a comprehensive interview and their medical histories were carefully documented. We also contacted their referring neurology clinics to verify if they were truly pwMS diagnosed using the McDonald criteria.[11] Prior sample size calculation was not performed, and therefore, no goal was set for the sample size.

In the vaccinated cohort, outcomes were obtained pertaining to an at-risk period (ARP) from the first dose until 2 weeks after the second, in which the vaccine is thought to implement its immunizing activity. To determine if the vaccine provoked MS relapses, we adopted the annualized relapse rate (ARR) of the unvaccinated pwMS, pertaining to a one-year period before the study—a measure of baseline MS relapsing activity in the respective time period—as our point of comparison. Obtaining the outcomes pertaining to one year before vaccination of the vaccinated pwMS—and therefore, their baseline ARR—was considered to enable self-controlled analysis, but unfortunately, it was not implemented due to a miscommunication. All variables and their measurements are summed up in Table 1. An MS relapse was defined as development of new or worsening of preexisting neurological symptoms, lasting for at least 24 hours without concurrent fever/infection and after at least 30 days of neurological improvement/stability. Our nurse was trained not to directly ask the participants if they had relapses, but to indirectly obtain information on the neurological symptoms, including their onset, severity, duration, characteristics, associations etc. After obtaining this information, the neurological symptoms that were in accordance with our definition of relapse were considered as relapses, and were validated by further information e.g. requirement of hospitalization or receipt of intravenous therapy.

Table 1. Study variables and their measurement.

Variable	Measurement
Primary outcome	
1. Number of MS relapses	Count
Secondary outcomes	
2. General post-vac symptoms	Categorical
3. Neurological post-vac symptoms	Categorical
4. Possible serious events	Count
5. Reason for vac-hesitancy	Nominal
Other	
6. Duration since the first dose	Number of weeks
7. Age	Years
8. Sex	Female/male
9. Disease duration	Years
10. MS type	Relapsing-remitting/progressive
11. Disease-modifying therapy	Categorical
12. Number of Comorbidities	Count
13. Previous COVID-19	Binary

Abbreviations: vac, vaccination; MS, multiple sclerosis.

Baseline characteristics of the vaccinated and unvaccinated cohorts were compared using proper (non)parametric statistical tests, including Student's T, Pearson Chi-square (with post-hoc residuals analysis in case the contingency tables were larger than 2-by-2), and Mann-Whitney U. Among the vaccinated pwMS, a multivariable logistic regression model was used to investigate the effect of age, sex, presence of comorbidities, MS type and duration, DMTs, and presence each general post-vaccination symptoms on development of neurological post-vaccination symptoms. The effects of age, sex, MS duration, MS type, DMTs, and vaccination on MS relapse rates, were investigated using a multivariable Poission regression model offset by the ARP of each participant i.e. the vaccine-related ARP for the vaccinated and the usual baseline ARP (prior year) for the unvaccinated pwMS. A two-tailed P value of 0.05 was considered as the threshold for diagnosis of statistical significance. Analyses were carried out using SPSS23 (IBM Inc.) for MacOS.

Results

1491 people participated in our online survey, 691 of whom were included in the study after going through the interviews (Figure 1). At the time of the interviews, 174 of the participants were unvaccinated, 100 received only one dose, and 417 were completely vaccinated (Table 2). The vaccinated and unvaccinated cohorts differed regarding their duration of MS ($P < 0.01$), previous COVID-19 history ($P < 0.01$) and their DMTs ($P = 0.05$) (Table 2). A greater portion of pwMS were on no DMTs in the unvaccinated cohort, and a greater portion were on high-efficacy DMTs in the vaccinated cohort.

84(16.2%) of the vaccinated participants experienced at least one post-vaccination neurological symptom, among which motor symptoms and vertigo were more common (Table 3). Presence of comorbidities (B [SE]: 0.76 [0.30], $P = 0.01$), receiving natalizumab therapy (B [SE]: 2.63 [1.24], $P = 0.03$), and experiencing post-vaccination myalgia (B [SE]: 0.73 [0.28], $P < 0.01$), predicted the development of post-vaccination neurological symptoms in the multivariable logistic regression model. Five vaccinated women with MS (two secondary progressive and three relapsing-remitting) experienced neurological symptoms during the ARP that met the criteria for an MS relapse, two were on dimethyl fumarate, one on glatiramer acetate, one on fingolimod, and one on rituximab therapies. One of the relapses followed the first and four followed the second dose of the vaccine. All relapses were followed by either partial or complete improvement after treatment with corticosteroids. The relapse rate (count per person-year) of vaccinated pwMS in their vaccine-related ARP was 0.10 and the ARR (count per person-year) of unvaccinated pwMS in the prior year was 0.07. The multivariable Poisson regression model failed to indicate a significant difference between relapse rates during the vaccination-related ARP of vaccinated pwMS and the ARR of unvaccinated pwMS in the prior year (Table 4). Although we used multivariable analysis to even out the possible bias, this result remains to be validated by further replications as the baseline characteristics—especially DMTs—of vaccinated and unvaccinated pwMS were not similar

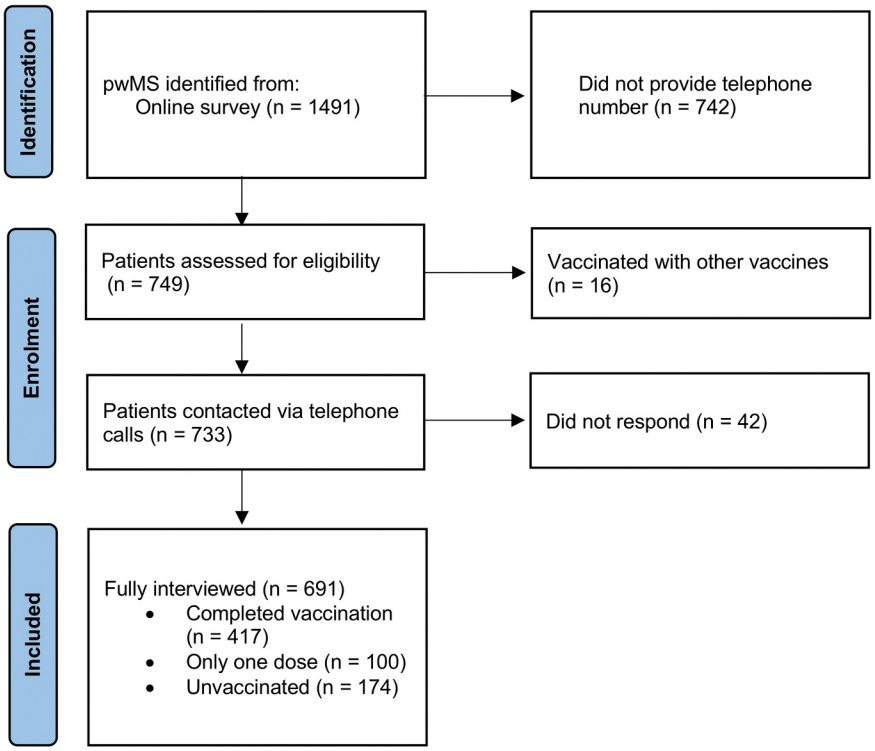

Figure 1. Study flow diagram.

Table 2. General characteristics of participants.

General characteristics	Vaccinated (n = 517)	Unvaccinated (n = 174)	*P*
Mean age (SD) [years]	37.81 (8.74)	36.75 (10.20)	0.19
Sex (n, %) [female/male]	397 (76.79)/ 120 (23.21)	137 (78.74)/ 36 (21.26)	0.18
Comorbidities (n, %)			0.62
• None	416 (80.46)	143 (82.18)	
• Hypertension	16 (3.09)	7 (4.02)	
• Diabetes	8 (1.55)	3 (1.72)	
• Smoking	5 (0.97)	2 (1.15)	
• Obesity	12 (2.32)	8 (4.59)	
• Autoimmune conditions	14 (2.71)	3 (1.72)	
• Thyroid dysfunction	38 (7.35)	9 (5.17)	
• Other	46 (8.90)	19 (10.92)	
Median MS duration (Range) [years]	8 (29)	6 (20)	<.01
MS phenotype (R/P)	427/90	154/20	<.01
History of COVID-19 (n, %) [Yes/No]	208 (40.23)/ 309 (59.77)	28 (16.09)/ 146 (83.91)	0.07
DMTs (n, %)			0.05
• No DMT	20 (3.87)	14 (8.04)	
• Interferons	161 (31.14)	50 (28.74)	
• Glatiramer Acetate	53 (10.25)	22 (12.64)	
• Dimethyl Fumarate	100 (19.34)	41 (23.56)	
• Teriflunomide	41 (7.93)	17 (9.77)	
• Fingolimod	48 (9.28)	14 (8.05)	
• Natalizumab	4 (0.77)	1 (0.57)	
• Rituximab	90 (17.41)	15 (8.62)	0.04*
Vaccination status (n, %)		NA	
• One dose	100 (19.3)		
• Two doses	417 (80.7)		
Median vaccine-related ARP (Range) [weeks]	6 (4)		

*The only significant post-hoc P-value with Bonferroni correction is reported.
Abbreviations: SD, standard deviation; R, relapsing; P, progressive; DMT, disease-modifying therapy; ARP, at-risk period; NA, not applicable.

(Table 2). Furthermore, apart from one case of COVID-19 and one case of ulcerative colitis flare—both after the first dose—no other serious adverse events were reported.

Table 3. Post-accination symptoms of participants during the ARPs.

	pwMS vaccinated with BBIBP-CorV		
Symptoms (n, %)	After first dose (n = 517)	After second dose (n = 417)	Total (n = 517)
GENERAL SYMPTOMS			
• No symptoms	222 (42.9%)	228 (54.7%)	137 (26.5)
• Fever	97 (18.8%)	56 (13.4%)	112 (21.66)
• Headache	122 (23.6%)	78 (18.7%)	147 (28.43)
• Myalgia	132 (25.5%)	84 (20.1%)	160 (30.95)
• Fatigue	106 (20.5%)	66 (15.8%)	123 (23.79)
• Hypersensitivity	55 (10.6%)	41 (9.8%)	70 (13.54)
• Pruritus	19 (3.7%)	12 (2.9%)	22 (4.26)
• Urticaria	3 (0.6%)	1 (0.2%)	3 (0.6%)
• Gastrointestinal	7 (1.4%)	0	7 (1.4%)
• Dyspnea	3 (0.6%)	0	3 (0.6%)
• Dizziness	5 (1%)	0	5 (1%)
• Other	15 (2.9%)	0	15 (2.9%)
NEUROLOGICAL SYMPTOMS			
• No symptoms	465 (89.94)	363 (87.05)	433 (83.7%)
• Motor	19 (3.68)	25 (5.99)	32 (6.2%)
• Sensory	11 (2.13)	10 (2.40)	12 (2.3%)
• Diplopia	8 (1.55)	11 (2.64)	14 (2.7%)
• Vision impairments	10 (1.93)	14 (3.36)	17 (3.3%)
• Vertigo	13 (2.51)	19 (4.56)	23 (4.4%)
Other	10 (1.93)	15 (3.60)	19 (3.7%)

Abbreviations: pwMS, people with multiple sclerosis.

Among the unvaccinated pwMS, the main reason for vaccination hesitancy was reported to be fear of possible adverse events (n = 145, 83.33%). Other reasons included pregnancy and lactation-related reasons (n = 8, 4.60%), believing that they have already obtained immunity after contracting COVID-19 (n = 7, 4.02%), waiting for other types of vaccines (n = 3, 1.72%), fears of conspiracy (n = 4, 2.30%), disbelieving vaccination (n = 6, 3.45%), and unawareness of eligibility (n = 1, 0.57%).

Table 4. Results of multivariable Poisson regression.

	Multivariable Poisson regression (n = 691, outcome: MS relapse, Offset: ARP)		
Predictors	B	SE	*P*
Age (per year)	−0.037	0.026	0.157
Sex			
• Male	(ref)		
• Female	−0.094	0.576	0.871
History of COVID-19			
• No	(ref)		
• Yes	0.404	0.564	0.473
MS type			
• Relapsing	(ref)		
• Progressive	0.160	0.723	0.824
MS duration (per year)	0.054	0.050	0.283
DMT			
• No DMT	(ref)		
• Injectables (IFN, GA)	−0.251	1.200	0.834
• Orals (DMF, TFN, FNG)	0.565	1.116	0.612
• Infused (RTX, NTZ)	0.541	1.214	0.656
Cohort			
• Unvaccinated	(ref)		
• Vaccinated	0.163	0.579	0.779

Abbreviations: MS, multiple sclerosis; ARP, at-risk period; ref, reference; DMT, disease-modifying therapy; IFN, interferons; GA, glatiramer acetate; DMF, dimethyl fumarate; TFN, teriflunomide; FNG, fingolimod; RTX, rituximab; NTZ, natalizumab.

Discussion

Subject to replication, our results suggest that the BBIBP-CorV vaccine does not increase the risk of relapse in pwMS, although a relatively small proportion of vaccinated pwMS may experience neurological symptoms. 83.7% of our participants did not develop any neurological sequelae following vaccination, and only 5 (0.97%) experienced post-vaccination MS relapses.

In a relatively similar cohort of 555 pwMS vaccinated with BNT162b2, followed up 14–21 days after the second dose of the vaccine, 13 (2.3%) acute MS relapses were reported.[6] In another study on 29 pwMS vaccinated with ChAdOx1 and four with BNT162b2, no lasting neurological adverse event or MS relapse was observed in at least two months of follow-up.[12] Similar to the present study, a more recent study on Iranian pwMS receiving the first dose of BBIBP-CorV also did not find an association between vaccination and short-term MS activity, although five post-vaccination MS relapses were reported.[7] Whether or not the mentioned relapses could be attributed to COVID-19 vaccines is unclear.

The BBIBP-CorV is an inactivated virus, administered in a two-dose regimen.[13] Its phase 1 and 2 trials and a study on a cohort of 89 non-MS individuals found no neurological adverse event or serious side effect.[14,15] In its phase 3 trial, apart from injection-site reactions, myalgia and headache were the most frequent systemic adverse events; five individuals experienced more severe systemic adverse events affecting the nervous system.[16] Systemic adverse events were more frequent after the first dose than the second in our study. Nevertheless, numerous studies have shown promising results in pwMS following the administration of inactivated vaccines (e.g., influenza or tetanus toxoid vaccines).[17–19]

Limited data is available to date on the clinical efficacy of vaccines in reducing COVID-19 incidence and severity among pwMS. This issue is of crucial value given the documented hindering effect of some DMTs—namely sphingosine 1-phosphate receptor (S1PR) modulators and anti-CD20 therapies (aCD20) – on proper immunization against COVID-19.[20,21–27] Accordingly, the limited available evidence pointed toward lower clinical efficacy of mRNA[28] and BBIBP-CorV[29] vaccines in pwMS on S1PR modulators and aCD20, however, further replications are required to validate these findings.

The reasons for vaccination hesitancy among the present study's cohort of unvaccinated pwMS clarifies the role of misinformation in preventing pwMS from getting vaccinated. Providing evidence-based consultations and reasoning by their neurologists is an encouraged strategy to encounter misinformation among the pwMS. Setting mandates is the next possible option, although it may not be required if the pwMS are provided adequate evidence-based information.

In conclusion, the BBIBP-CorV COVID-19 vaccine seems relatively safe to administer in pwMS as it does not seem to evoke severe neurological symptoms or MS relapses. Like other COVID-19 vaccines, its efficacy among pwMS remains to be investigated in more controlled studies.

Limitations

Several limitations apply to this work because of its remote nature: I) considering the limited framework of the study, we could not review the participants' medical records to perform self-controlled analyses; We did consider obtaining retrospective data regarding the relapses of vaccinated pwMS before their vaccination; we regret that this was not done due to a miscommunication; II) the outcome measurements were performed in a retrospective and self-reporting manner, which might not have been accurate and might have caused recall bias; III) The comparison of relapse rates in the six-week vaccination-related ARP of the vaccinated pwMS, with the ARR of the unvaccinated ones may not have been thoroughly justified, as they differed in their baseline characteristics and especially, the DMTs they were receiving; We tried to even out the possible bias by using multivariable analysis, still, more studies will be required to validate the results; IV) the remote nature and the short observation period of our study increases the probability of possibly missed relapses, which might have been the cause for the relatively low relapse frequency in our study; V) Due to the self-reporting nature of the study, the probability of recall bias should be acknowledged, especially for the unvaccinated cohort, as for whom the relapse data was gathered retrospectively pertaining to a relatively-long period of one year; VI) As sample size calculation was not done, the study power may not have been adequate; VII) 100 vaccinated pwMS did not receive their second doses and were still in the vaccination-related ARP when they were interviewed, and hence, no information is available regarding their possible sequelae following their second dose; and VIII) the study lacked precise clinical and paraclinical evaluations for verification of relapses, had a short post-vaccination follow-up, and was based on remote self-reporting of the pwMS, therefore, further replication with longer follow-ups and on-site clinical and paraclinical evaluations is encouraged to confirm the results.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured inthis article.

ORCID

Hosein Nouri http://orcid.org/0000-0003-1808-0443
Mehri Salari http://orcid.org/0000-0001-7102-821X
Nahad Sedaghat http://orcid.org/0000-0002-2796-6791

Data availability statement

The anonymized data will be shared with any qualified investigator upon reasonable request.

Ethics

This study was approved by the ethics committee of Isfahan University of Medical Sciences. Considering the remote nature of the study, written consent could not be obtained from the participants, although they were completely informed about the aims of this study and all conveyed consent for anonymized publication of their information, both in the online surveys and on the telephone calls. No deanonymized data was stored by the investigators in any way, to ensure the privacy protection of the participants.

Publication history

Preprint in medRxiv (https://doi.org/10.1101/2021.10.17.21265114).

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